REMARKS

Claims 41, 44, 46 and 55-58 are pending in the subject application. No claim has been added, canceled, or amended herein. Accordingly, claims 41, 44, 46 and 55-58 are still pending and under examination.

Claim objection

The Examiner objected to claim 55 for reciting or encompassing a non-elected invention. Specifically, the Examiner alleges that claim 55 recites, in part, a "bone marrow cell."

In response, applicants note that, as amended in the July 9, 2002 Amendment and acknowledged by the Examiner in the November 19, 2002 Final Office Action, claim 55 was amended such that it no longer recites a "bone marrow cell." Accordingly, applicants maintain that the Examiner's objection of claim 55 is obviated.

Rejection under 35 U.S.C. §103

The Examiner rejected claims 41, 44, 46, 55 and 56 as allegedly obvious over Yan et al., in light of Hale et al. and Heaney et al.

Claim 41, and dependent claims 44, 46 and 55-56, provide a method of inhibiting the binding of a β-sheet fibril to RAGE on the surface of a cell of a subject, wherein the cell is located outside the central nervous system of the subject, which comprises contacting the cell with a compound that inhibits binding of the β-sheet fibril to RAGE.

Specifically, the Examiner alleges that Yan et al. teach that amyloid

beta peptide binds to the receptor for RAGE. They also demonstrate that binding of amyloid to the RAGE receptor induces oxidative stress, activation of microglia and activation of inflammatory pathways involving transcription factor NF-kB. Yan et al. further suggest that these processes may contribute to the cellular pathologies seen in Alzheimer's disease. However, Yan et al. do not teach the inhibition of binding between amyloid beta and RAGE.

Hale et al. teach the inhibition of tumor necrosis factor using the soluble form of its receptor, and that soluble tumor necrosis factor receptors were effective in inhibiting the effect of tumor necrosis factor in culture, as well as in several models of sepsis in mice and baboons. Heaney et al. give numerous examples in which soluble receptors are involved in intracellular signaling and conclude that "construction and development of soluble receptors as pharmaceuticals may be useful to specifically inhibit or facilitate hormone action in disease states." In light of these references, the Examiner alleges that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the soluble form of RAGE to inhibit binding of amyloid peptide that is known to bind to the receptor for AGE on the surface of cells.

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, must teach or suggest every limitation of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at

the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Applicants maintain that Yan et al., in view of Heaney et al. and Hale et al., fail to create a reasonable expectation of success.

According to the M.P.E.P. §2143.01,

> "[t]he mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination."

In re Mills, 916 F.2d 680 (Fed. Cir. 1990) (emphasis added). Applicants assert that Hale et al. describe the inhibition of the binding of only *one* type of receptor through competitive binding, namely the inhibition of the receptor for tumor necrosis factor by recombinant human soluble Type I and Type II TNF receptors. Nowhere do Hale et al. teach or suggest the inhibition of binding of other receptors by the soluble form of their receptors. Applicants assert that one skilled in the art cannot reasonably expect that, given the successful inhibition of only one receptor by the soluble form of that receptor, *all* receptors would necessarily be inhibited by the soluble form of their receptor. Furthermore, Heaney et al. state that not all soluble receptors will be expected to inhibit binding of the ligand to the membrane-associated receptor. Specifically, Heaney at al. state that "[t]he physiologic roles of the soluble receptors are incompletely understood . . ." and that in one model, "the soluble receptor has no intrinsic role in signal transduction and functions to prevent degradation of the ligand until it is

delivered to the membrane-associated receptor." (See page 1946, second paragraph). Accordingly, given the teachings of Heaney et al., one skilled in the art cannot reasonably expect that soluble RAGE will inhibit the binding of amyloid peptide to RAGE on the surface of a cell. Devoid of any support to the contrary, an "invitation to try," which applicants do not concede exists, is considered inadequate support for an obviousness rejection. (*O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988))

Rejections under 35 U.S.C. §112, First Paragraph

The Examiner also rejected claims 41, 44, 46, 55 and 56 under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

Specifically, the Examiner alleges that while the specification is enabling for a method of inhibiting binding of β-amyloid to RAGE in vitro, it does not reasonably provide enablement for inhibiting binding of β-amyloid to RAGE in vivo.

In response, applicants respectfully traverse the Examiner's rejection. In support of their traversal, applicants incorporate their remarks regarding enablement made in the July 9, 2002, January 7, 2002 and August 19, 2003 Amendments, and make the following additional remarks to underscore their position.

The test for enablement under 35 U.S.C. §112, first paragraph, is whether the disclosure contains sufficient information regarding the subject matter of the claims to enable one skilled in the relevant art to practice the claimed invention without undue experimentation.

Applicants maintain that the specification is enabling for a method for inhibiting binding of β-amyloid to RAGE in vivo. Specifically, the specification recites "[i]n a model of systematic amyloidosis, blockage of fibril-RAGE interaction *in vivo* suppressed cellular stress and amyloid A fibril accumulation" (See page 57, lines 17-20). Experimental details for the *in vivo* administration of sRAGE to a murine model of systemic amyloidosis is also described on page 62, lines 22 to page 63, line 12. Furthermore, the specification indicates that in an *in vivo* model of systemic amyloidosis, blockage of fibril-RAGE interaction suppressed cellular stress and amyloid A fibril accumulation, suggesting that cell surface RAGE is a focal point for interaction with fibrils, which renders amyloid pathogenic by a receptor-dependent mechanism (See page 74, lines 1-31). Therefore, the specification teaches that in a mouse model of systemic amyloidosis, the *in vivo* administration of sRAGE blocks amyloid fibril-RAGE interaction and suppressed cellular stress and amyloid A fibril accumulation in tissues. Accordingly, applicants maintain that the specification is enabling for a method of inhibiting binding of β-sheet fibril to RAGE on the surface of a cell located outside the central nervous system.

The Examiner further bases her rejection on the unpredictability in the art for treating dementia and the lack of guidance regarding the specific activity of sRAGE in humans. Applicants note that claim 41, and dependent claims 44, 46, 55 and 56, do not provide a treatment for dementia, but rather provide a method of inhibiting the binding of a β-sheet fibril to RAGE on the surface of a cell of a subject, wherein the cell is located outside the central nervous system of the subject, which comprises contacting the cell with a compound that inhibits binding of the β-sheet fibril to RAGE.

Furthermore, applicants are not aware of any requirement under 35 U.S.C. §112, first paragraph, that mandates providing human experimental data in the specification in order to enable the subject claims. Applicants maintain that the in vivo experiments described in the specification adequately enable the claimed methods. The Examiner has not cited any art which indicates that such data are insufficient for enabling the subject claims.

Accordingly, applicants maintain that claims 41, 44, 46, 55 and 56 satisfy the requirements of 35 U.S.C. §112, first paragraph.

The Examiner also rejected claims 57 and 58 under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

Claim 57 provides a method of inhibiting the binding of β-sheet fibril to RAGE on the surface of a cell of a subject, wherein the cell is located outside the central nervous system of the subject, which comprises administering to the subject an amount of soluble RAGE (sRAGE) effective to inhibit binding of the β-sheet fibril to RAGE.

Claim 58 provides a method of inhibiting the interaction of a β-sheet fibril to RAGE on the surface of a cell of a subject, wherein the cell is located outside the central nervous system of the subject, which comprises administering to the subject an amount of a peptide fragment of sRAGE identical to the V-domain of sRAGE effective to inhibit binding of the β-sheet fibril to RAGE.

In response, applicants respectfully traverse the Examiner's rejection. In support of their traversal, applicants incorporate their remarks made in the July 9, 2002 and January 7, 2002 Amendments

regarding enablement, and make the following additional remarks to underscore their position.

Specifically, the Examiner states that nowhere in the specification is a nexus described between inhibition of binding of amyloid and a disease state. The Examiner further states that Alzheimer's disease is highly unpredictable and using the methods described to obtain any clinical effect would require undue experimentation.

Again, the test for enablement is whether the disclosure contains sufficient information to enable one skilled in the relevant art to practice the claimed invention without undue experimentation.

Applicants maintain that the disclosure is sufficient to enable one skilled in the art to practice the claimed methods of binding inhibition. Applicants note that the claimed methods do not provide a method for the treatment of Alzheimer's or any other disease, but rather a method for inhibiting the binding of β-sheet fibril to RAGE. Although the claimed methods may eventually play a role in the treatment of certain diseases, the treatment of such are not explicitly recited in the rejected claims. Applicants maintain that there is no requirement under 35 U.S.C. §112, first paragraph, for showing efficacy in treating a disease when such a method is not claimed. For the above reasons, applicants maintain that claims 57 and 58 satisfy the provisions of 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner also rejected claims 41, 44, 46 and 55-58 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to point

out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Examiner alleges that the claims encompass a method of using sRAGE for preventing the interaction of an amyloid-forming peptide with RAGE. However, the Examiner alleges that there is no recognized structural or functional determinants in the claims such that the molecules encompassed can be distinguished from any other molecule.

In response, applicants respectfully traverse. The specification identifies the metes and bounds of the claimed invention by disclosing the structural and functional determinants of sRAGE such that it can be distinguished from other molecules.

Applicants maintain that the specification is not indefinite. The specification recites that a compound used to inhibit the binding of a β-sheet fibril to RAGE on the surface of a cell may be sRAGE or a fragment thereof, including the isolated peptide having an amino acid sequence corresponding to the V-domain of RAGE (See page 18, lines 31-35 and page 19, lines 25-28). Furthermore, the specification recites that Neeper et al. (1992) disclose the full length amino acid sequence of RAGE, as well as the highly conserved 120 amino acid V-domain (See page 21, lines 1-11). Therefore, applicants maintain that the specification discloses the highly conserved structure and function of RAGE, including the invention. Accordingly, applicants maintain that claims 41, 44, 46 and 55-58 are not indefinite and meet the requirements of 35 U.S.C. §112, second paragraph.

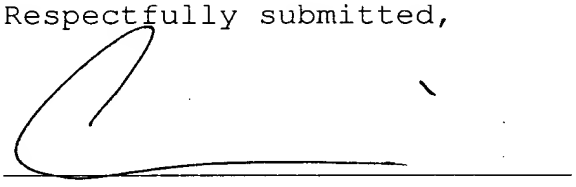
Summary

Based on the reasons set forth hereinabove, applicants maintain that the pending claims are in condition for allowance. Accordingly, allowance is respectfully requested.

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

Respectfully submitted,



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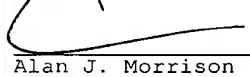

10/7/04

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